Stem cell-based carriers for RCR vector delivery to glioblastoma

Grant Award Details

Stem cell-based carriers for RCR vector delivery to glioblastoma

Grant Type: Early Translational II

Grant Number: TR2-01791

Project Objective: Project aims to develop a human mesenchymal stem cell (hMSC-based carrier system for tumor-homing delivery of a replication-competent retrovirus (RCR) vector expressing the yeast cytosine deaminase (CD) prodrug activator enzyme.

Investigator:

Name:	Noriyuki Kasahara
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Brain Cancer, Cancer, Solid Tumors

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: $3,340,625

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE (Year 4)

View Report

Grant Application Details

Application Title: Stem cell-based carriers for RCR vector delivery to glioblastoma

Public Abstract:

Modified viruses can be used to infect tumor cells and alter the tumor cell to make anti-tumor proteins. Most researchers use virus that can infect and modify the tumor cell it enters, but can not make more of itself to infect additional cells surrounding the original infected cell. This type of virus is called replication-incompetent virus. Use of replication-incompetent virus is considered safe because no additional virus, which potentially could get out of control, is generated inside of the tumor. However such therapies have been shown to have only limited beneficial effects, presumably because too many tumor cells never get infected.

Newer approaches investigate the use of replication-competent viruses to achieve highly efficient gene transfer to tumors. A successfully transduced tumor cell itself becomes a virus-producing cell, sustaining further transduction events even after initial administration. We propose here to use a type of replication-competent virus that only infects dividing cells and therefore will infect the rapidly dividing cancer cells but not normal brain cells.

The use of replication-competent virus is potentially more risky but is well justified in clinical scenarios involving highly aggressive and rapidly progressing metastatic tumor growth in the brain. To administer therapeutic virus into the brain, the virus is injected right into the center of the tumor. Yet, human brain tumors are often found as diffusely spreading foci in the brain and may be difficult to eliminate by locally-administered replication-competent retrovirus (RCR) vectors alone.

In this study we propose to use a type of adult stem cell called a "mesenchymal stem cell" (MSC) as a delivery system for the RCR vectors. Mesenchymal stem cells (MSCs) have been shown to have natural tumor-homing abilities, and can migrate to tumor foci and penetrate through into the interior of tumor masses. We propose to engineer them into "aircraft carriers" that release tumor-selective viruses, which can then efficiently spread suicide genes from one cancer cell to another in multiple tumor foci in the brain.

Statement of Benefit to California:	This research is based on a solid foundation that combines two innovative technologies for the treatment of primary brain tumors, particularly glioblastoma multiforme (GBM) the most malignant form of brain tumor, which afflicts men, women, and children in California and elsewhere. Each of these technologies has been approved separately by FDA for clinical testing in humans: human mesenchymal stem cells (MSCs), and replication-competent retrovirus (RCR) vectors. MSCs have been reported to exhibit a natural ability to migrate to solid tumors and penetrate into the tissue mass. Once inside a tumor, RCR vectors can spread selectively in the cancer cells and their replication can keep up with their uncontrolled proliferation, and their ability to integrate themselves into the cancer cell genome allows them to permanently "seed" tumor cells with therapeutic genes. Here we propose to utilize the natural tumor homing ability of MSCs to deliver RCR vectors into brain tumors. This "virus vs. cancer" strategy takes advantage of the amplification process inherent in the spread of virus from cell to cell, and by using MSCs to initiate the virus infection efficiently in brain tumors, represents an approach that will have the potential to effectively treat this poor prognosis disease. If successful, clinical application of this strategy can be implemented by an "off-the-shelf" mesenchymal stem cell (MSC) primary cell lines that have been pre-characterized for their tumor homing ability and virus production capability, and can be offered to patients without requiring an invasive procedure to harvest their own stem cells. Furthermore, this represents a treatment that could potentially be administered through a needle, thus making it unnecessary for patients to undergo major neurosurgical procedures entailing craniotomy at an advanced medical center. Hence this research could lead to a novel treatment approach that would particularly address the needs of brain tumor patients in California who are underserved due to socioeconomic and geographic constraints, as well as the elderly who are poor-risk for surgical interventions.

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